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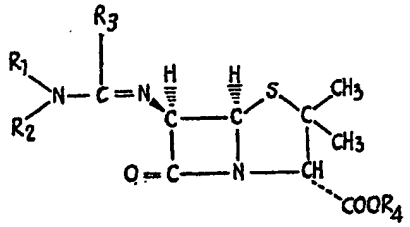
(19)

(54) PENICILLANIC ACID DERIVATIVES

(71) We, LØVENS KEMISKE FABRIK PRODUKTIONSAKTIESELSKAB, a Company incorporated under the Laws of Denmark, of 2750 Ballerup, Denmark, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement: —

This invention relates to hitherto unknown derivatives of 6-aminopenicillanic acid, to pharmaceutically acceptable salts thereof, and to methods for the production of these new compounds.

The compounds of the invention have the general formula:



in which R_1, R_2 and R_3 each represent an aliphatic hydrocarbon radical, a mono- or bicyclic aryl radical, an aralkyl radical, a cycloalkyl radical, a cycloalkyl-alkyl radical, a heterocyclic radical, or a heterocyclically substituted alkyl radical; R_1 and R_2 when taken together with the nitrogen atom may represent a ring system; R_1 and R_3 when taken together with the N—C atoms may represent a ring system; R_1, R_2 and R_3 are optionally substituted; R_4 represents a hydrogen atom, or an unsubstituted or substituted alkyl or aralkyl radical.

In particular, R_1, R_2 and R_3, which may be the same or different, may each represent an aliphatic hydrocarbon radical in which the carbon chain can be straight or branched, saturated or unsaturated, e.g. a methyl, ethyl, propyl, isopropyl, butyl, sec.butyl, tert.butyl, pentyl, hexyl, dodecyl, allyl, butenyl, pentenyl or propargyl radical; a mono- or bicyclic aryl radical, e.g. a phenyl or naphthyl radical; an aralkyl radical, such as a mono- or bicyclic aralkyl radical, e.g. a benzyl, phenylethyl or 1- or 2-naphthyl-methyl radical; a cycloalkyl or cycloalkyl-alkyl radical, in which the cycloalkyl group can have from 3 to 10 ring members and can be saturated or have one or two double bonds, e.g. a cyclopentyl, cyclohexyl, 1-adamantyl, 1-bicyclo (2,2,2,)octyl, cyclopentenyl, cyclohexenyl, cyclopentylmethyl, cyclohexylmethyl, cyclopentylethyl or cyclohexenylmethyl radical; a heterocyclic radical or a heterocyclically substituted alkyl radical in which the heterocyclic part can be more or less hydrogenated and can have from 5 to 10 atoms in the ring and can contain oxygen, sulphur, or nitrogen atoms, e.g. a pyridyl, pyrazinyl, pyrimidyl, pyrrolidyl, piperidyl, morpholinyl, thiazinyl, furyl, thienyl or quinolyl radical, in all of which the hetero atoms may be placed in any of the available positions; R_1 and R_2 when taken together with the nitrogen atom and R_1 and R_3 when taken together with the N—C atoms may represent heterocyclic radicals having from 5 to 10 atoms and optionally containing other hetero atoms in the ring, such as sulphur, oxygen or nitrogen forming more or less hydrogenated ring systems e.g. a piperidyl, morpholinyl, hexahydro-1H-azepin-1-yl, or hexahydro-1(2H)-azocinnyl radi-

cal. The radicals R_1, R_2 and R_3 may be further substituted with one or more halogen atoms, and alkyl, hydroxy, alkoxy, carbocyclic aryloxy, alkylthio, carbocyclic arylthio, acyl, carboxy, carbalkoxy, carbamyl, carbamido, cyano, sulphonyl, azido, amino- or substituted amino radicals.

In particular R_4, when representing an alkyl radical, or an aralkyl radical preferably stands for a C_1 to C_7 alkyl or aryl- C_1 to C_3 alkyl radical or an alkyl radical substituted with halogen, or cyano; e.g. a methyl, ethyl, benzyl, chloro-methyl, β,β,β-trichloroethyl, or cyanomethyl radical; R_4 may further represent an acyloxymethyl radical the acyl part of which is a C_1 to C_5 alkanoyl, or aromatic acyl radical, such as an acetyl, propionyl, butyryl, pivaloyl or benzoyl radical.

The compounds of formula I may be isolated as such or in the form of a salt with a pharmaceutically acceptable acid, such as hydrochloric acid, phosphoric acid, nitric acid, p-toluenesulphonic acid, acetic acid, propionic acid, citric acid, tartaric acid or maleic acid. When R_4 stands for a hydrogen atom the compounds of formula I may be isolated as the amphoion (zwitterion) or as a salt, e.g. an alkali metal salt or an ammonium or amine salt or as a salt with a strong acid.

The invention comprises all possible isomeric forms of the compounds of formula I, depending upon the different substituents, whereas the 6-aminopenicillanic acid moiety has the configuration of that obtained by a fermentation process.

The compounds of the invention possess valuable antibacterial activity and the toxicity is extremely low.

The antibacterial effect of the new compounds is advantageous compared to other penicillins such as penicillin-G in that the new compounds are more resistant to enzymatic degradation by microorganisms.

In an *in-vitro* experiment, strains of *Staphylococcus aureus, Bacillus cereus, Klebsiella pneumoniae* and *Proteus vulgaris* were grown overnight at 37°C, in an NIH-bouillon ("Difco" (registered Trade Mark)). To the outgrown culture, an amount of 10 ug. of penicillin-G, the compound of Example 1 hereafter and the compound of Example 8 hereafter respectively, were added per ml. of the substrate and incubated at 37°C. Samples were taken at certain intervals and the residual-activity was measured microbiologically. The half-life for the compound of Example 1 and the compound of Example 8 were at least 15 times longer than that of penicillin-G. Before the above experiments, the compounds of Example 1 and 8, both of them being esters, were subjected to an enzymatic cleavage yielding the corresponding free acids.

In the Table below is shown the antibacterial spectrum of the acid, 6-(N,N-diethyl-2′-phenoxyacetamidino-N′)-penicillanic acid, which corresponds to the ester prepared according to Example 20 and which is obtained from this ester by an enzymatic hydrolysis by treatment with a 20 per cent mouse serum at 37°C. and at a pH of 7.5 in 90 minutes. In the Table IC_{50} means the concentration required for 50 per cent inhibition.

TABLE

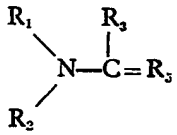
Strains	10_{50} (μg/ml)
Staph. aureus, penicillin sensitive	0.050
Staph. aureus, penicillinase producing	>100
Diplococcus pneumoniae	0.020
Streptococcus pyogenes	0.016
Escherichia coli	16
Klebsiella pneumoniae	32
Proteus vulgaris	0.50
Salmonella typhimurium	>100
Neisseria gonorrhoeae	0.13
Neisseria meningitidis	0.20

The antibacterial effect of the compounds of this invention is quite unexpected, since hitherto only derivatives of 6-aminopenicillanic acid substituted in the 6-amino-group with an acyl group have shown an antibacterial effect.

For certain medical purposes it will be advantageous to use the present compounds in the form of the free acids or their salts, whereas for other purposes it will be more favourable to use the easily hydrolyzable esters, which will be chemically or enzymatically hydrolyzed to the corresponding free acids in the organism. In other cases, the less hydrolyzable esters will be preferred in order to obtain particular distribution in the body.

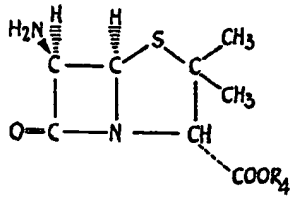
For instance in some cases the afore-mentioned acyloxymethyl esters of formula I are absorbed more efficiently after oral administration than the corresponding free acids. After absorption, these esters are hydrolyzed under the influence of enzymes present in blood and tissues with the liberation of the corresponding free acids, which generally have a more pronounced antibacterial activity than the esters.

The invention also comprises methods for the preparation of the above described compounds. In one method, the compounds are prepared by reacting an acid amide halide, an acid amide dialkyl sulphate complex or an acid amide acetal or thioamide acetal or acid thioamide alkyl halide complex or similar reactive derivative of an amide or a thioamide of the general formula II:



(II)

in which R_1, R_2 and R_3 have the meanings defined above and R_5 stands for oxygen or sulphur, with a 6-amino-penicillanic acid derivative of the general formula III:



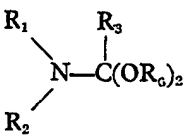
(III)

in which R_4 has the meaning defined above or with a silyl ester of 6-aminopenicillanic acid. In the latter case, the reaction must be followed by a solvolysis to provide the compounds of the invention in which R_4 is hydrogen, which also may be obtained by cleavage of the other esters.

The starting materials of formula II are known or can be prepared by methods known from generally used textbooks.

The amides of formula II can by transformed by well-known methods into reactive derivatives such as acid amide halides, acid amide dialkyl sulphate complexes or acid amide acetals. The acid amide halides used are preferably the chlorides or bromides, and they can be prepared by treating the amides with halogenating agents. It is preferred to use halogenating agents which, throughout the reaction, form gaseous by-products, such as phosgene, oxalyl halides, or thionyl halides, but others may also be used. The reaction can be performed in an inert, dry, organic solvent, e.g. ether or toluene, in which the amide halide will in most cases be insoluble and from which it can be isolated by filtration after the reaction is completed. The acid amide halides are hygroscopic and rather unstable and are therefore preferably used in the next step without purification.

The acid amide dialkyl sulphate complexes can be prepared by treating the amides with a dialkyl sulphate, preferably dimethyl sulphate, under well-known conditions. By treating the acid amide dialkyl sulphate complexes with sodium lower alcoholates, e.g. sodium methoxide, acid amide acetals of the general formula IIa:



(IIa)

in which R_1, R_2 and R_3 have the meanings defined above and R_6 is a C_1 to C_7 alkyl radical, are formed, which acetals may also be used in the next step. Thus, a solyl ester of 6-aminopenicillanic acid may be reacted with an amide acetal of formula IIa, whereafter the silyl ester of the reaction product is hydrolysed or alcoholysed to form the compound of formula I in which R_4 is a hydrogen atom.

When acid thioamides are used as starting materials, a reactive derivative in the form of an acid thioamide alkyl halide complex can be formed by treatment with an alkyl halide, e.g. a lower-alkyl iodide. This reaction is well-known from the chemical literature.

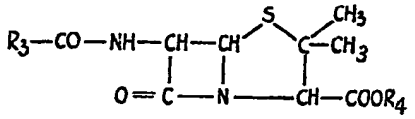
The reaction conditions for the reaction between the amide derivative and the compound of formula III depend upon the reaction components used in the process. When acid amide acetals are used in the reaction with the compounds of formula III, the reaction temperature depends upon the reaction components. The reaction is performed in an inert organic solvent, for instance ether.

When acid amide halides, dialkyl sulphate complexes, or thioamide alkyl halide complexes are used, the reaction is also performed in an inert organic solvent, which is dry and free from traces of alcohols, preferably chloroform, in which the reaction components are soluble, but solvents in which the starting materials are insoluble, e.g. ether, may be used as well. The reaction is performed under cooling and in the presence of at least one equivalent of a tertiary amine, for example trimethylamine, triethylamine, N,N-diisopropylethylamine or N-methylmorpholine. In the case where one equivalent of the tertiary amine is used, the reaction product will be obtained as a salt when an acid amide halide is used, and as an R_1,R_2,R_3-amidinopenicillanic acid derivative when the dialkyl sulphate complexes and thioamide alkyl halide complexes are used. When two or more equivalents of the tertiary amine are used an R_1,R_2,R_3-amidinopenicillanic acid derivative will be obtained and can be transformed into a salt, if desired.

The reaction time depends upon the reactants, the temperature and the solvents used in the process. In the case where R_4 stands for a hydrogen atom, it is preferred to protect the carboxyl group as a trimethylsilyl ester or a dimethylsilyl diester which, after the reaction can easily be cleaved. This reaction is preferably performed with an acid amide acetal reactant.

The preparation of the silyl esters of 6-aminopenicillanic acid is known from the literature. The silyl esters of the amidinopenicillanic acids are preferably cleaved by hydrolysis or alcoholysis under mild conditions.

In another method, the compounds of the invention can be prepared by reacting an amine of the formula HNR_1R_2 with a reactive derivative as indicated below of a 6-acylaminopenicillanic acid ester. Such a reactive derivative is for instance obtained by reacting a compound of formula IV:



IV

in which R_3 and R_4 are as defined above, with a halogenating agent, E.G. phosphorous pentachloride, in the presence of a tertiary organic base, for instance quinoline. The reaction can be performed without isolation of the intermediate formed by the process, which in the example mentioned above is presumed to be an amide chloride of the compound of formula IV. The reactions are performed below or at room temperature and in the presence of an inert solvent, e.g. chloroform. Another reactive derivative of the compound of formula IV which can be used is an imido ester, which can be prepared by reacting the amide chloride mentioned above with a lower aliphatic alcohol in the presence of a tertiary organic amine, e.g. triethylamine.

The reaction products of formula I can be purified and isolated in conventional manner and may be obtained either in the free state or in the form of a salt. The free acid (R_4 = H) can also be obtained from some of the esters by an enzymatic hydrolysis or a mild hydrogenolysis, and, if the free acid is the reaction product, the esters can be prepared therefrom by methods known from the literature.

Some of the compounds of formula III are known compounds and may be prepared by esterification of 6-aminopenicillanic acid to a protected 6-aminopenicillanic acid such as the 6-trityl derivative thereof. The trityl group may be split off after the reaction under conditions not affecting the lactam ring. They can also be prepared by esterification of the generally industrially used penicillins, whereafter the acyl side

chain can be split off chemically or enzymatically under such conditions that the ester group is not affected.

The compounds of formula (I) are well tolerated compounds. In the case where R_4 is hydrogen, the compounds are preferably used for parenteral administration in the form of an aqueous, sterile solution. In the case where esters are used, they are preferably administered orally, either as such or in form of one of their salts, and may be mixed up with a solid carrier and/or auxiliary agent. In such compositions, the proportion of therapeutically active material to carrier substance and auxiliary agent can vary between 1% and 95%. The compositions can either be worked up into a pharmaceutical form of presentation, such as tablets, pills or dragees, or can be filled into medical containers such as capsules, or, in the case of mixtures, filled into bottles. Pharmaceutical organic or inorganic solid or liquid carriers suitable for oral, enteral or topical administration can be used to make up the composition. Gelatine, lactose, starch, magnesium stearate, talc, vegetable and animal fats and oils, gum, polyalkylene glycol, or other conventional carriers for medicaments are all suitable as carriers. Furthermore, the compositions may contain other pharmaceutically active components which can appropriately be administered together with the compounds of the invention in the treatment of infectious diseases, such as other suitable antibiotics.

The invention will be further described in the following non-limiting Examples.

Example 1

Pivalyloyloxymethyl 6-(N,N-dimethyl-phenylacetamidino-N)-penicillanate nitrate

14 ml. of a solution of phosgene in dry toluene, containing 2.2 g. of phosgene, was slowly added to a solution of 3.3 g. of N,N-dimethyl-phenylacetamide in 10 ml. of dry toluene with stirring and ice-cooling. Stirring was continued for 2 hours at room temperature, whereupon the amide chloride formed was quickly isolated by filtration with suction, washed with dry ether and kept in an exsiccator.

2.2 g. of the crude amide chloride were dissolved in 35 ml. of dry, alcohol-free chloroform. While stirring and maintaining the temperature at $-30°C.$, this solution was slowly added to a solution of triethylamine, (3.1 ml.) and pivalyloxymethyl 6-aminopenicillanate (3.3 g.) in 15 ml. of dry, alcohol-free chloroform. The temperature was raised to 0°C. during 3/4 hour. After evaporation *in vacuo*, the residue was triturated with 200 ml. of ether. The precipitate was removed by filtration and the filtrate evaporated *in vacuo*. The residue was dissolved in 250 ml. of ether and filtered using diatomaceous earth as a filter aid.

0.35 ml. of concentrated nitric acid was dissolved in 10 ml. of dry ethanol (caution!) and slowly added to the filtrate with stirring and ice-cooling. The precipitate formed was isolated and treated with 30 ml. of methylene chloride which left most of the nitrate of the unreacted pivaloyloxymethyl 6-aminopenicillanate undissolved. After filtration and evaporation *in vacuo* of the filtrate, the residue was twice recrystallized from acetone-ether yielding an analytically pure product with a melting point of 146.5—147°C.. $[\alpha]_D^{20}$: 187° (c=1, 96% C_2H_5OH).

Example 2

Pivaloyloxymethyl 6-(N,N-diethyl-thiophene-2-carboxamidino-N)-penicillanate

To a solution of N,N-diethyl-thiophen-2-carboxamide (3.7 g.) in dry ether (50 ml.) was slowly added oxalyl chloride (17 ml.) in dry ether (10 ml.) at 0°C. with stirring. The mixture was stirred for 3½ hours at room temperature. The precipitate was filtered off, washed with ether and stored in an exsiccator.

2.4 g. of the crude amide chloride were dissolved in dry alcohol-free chloroform (15 ml.). At a temperature of $-20°$ to $-30°C.$, this solution was added dropwise to a solution of pivaloyloxymethyl 6-aminopenicillanate (3.3 g.) and triethylamine (2.8 ml.) in dry chloroform (30 ml.) with stirring. The temperature was raised to 0°C. in the course of 3/4 hour. The solution was evaporated *in vacuo* and the residue treated with ether (250 ml.). After filtration to remove triethylamine hydrochloride, the filtrate was extracted with dilute hydrochloric acid (100 ml. at a pH of about 3) and the aqueous phase was made alkaline to a pH of about 7.5. The precipitate which formed was isolated and recrystallized from ethanol-water to yield the pure product with a melting point of 96—97°C.. $[\alpha]_D^{20}$: +110° (c=1, 96% ethanol).

Example 3

Pivaloyloxymethyl 6-(N,N-diethyl-β-carbomethoxypropionamidino-N)-penicillanate

To an ice-cold solution of N,N-diethyl-β-carbomethoxypropionamide (3.7 g.) in dry benzene (25 ml.) was slowly added 22 ml. of a solution of phosgene (4.0 g.) in dry benzene with stirring. The stirring was continued overnight at room temperature, whereupon the solvent and unreacted phosgene were removed *in vacuo* leaving an oil.

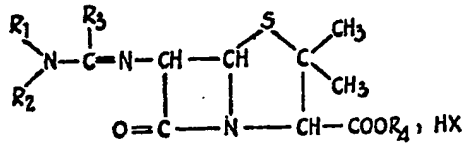
The oily amide chloride (2.7 g.) was dissolved in dry chloroform (15 ml.). This solution was added dropwise to a solution of pivaloyloxymethyl 6-aminopenicillanate (3.3 g.) and triethylamine (3.1 ml.) in chloroform (30 ml.) at −40°C. with stirring. The temperature was raised to 0°C. within 3/4 hour. The solution was evaporated *in vacuo* and the residue triturated with ether (200 ml.). The precipitate was filtered off and the filtrate extracted with dilute hydrochloric acid (100 ml., pH~3). The aqueous phase was made alkaline to a pH of about 7.5 and extracted with ethyl acetate (3 × 50 ml.). After drying, the organic phase was evaporated *in vacuo* leaving an oil which did not crystalize.

$N(CH_2CH_3)_2$	6H	t	at 1.12	(J=7)
$C(CH_3)_3$	9H	s	at 1.22	
$C_{(2)}(CH_3)_2$	3H	s	at 1.51	
	3H	s	at 1.67	
$=C-CH_2-CH_2-CO$	4H	broad singlet at 2.67		
$N(CH_2-)_2$	4H	q	at 3.34	(J=7)
OCH_3	3H	s	at 3.70	
$C_{(3)}H$	1H	s	at 4.41	
$C_{(6)}H$	1H	d	at 5.20	(J=4)
$C_{(5)}H$	1H	d	at 5.53	(J=4)
OCH_2O ABq	1H	d	at 5.78	(J=5.5)
	1H	d	at 5.90	(J=5.5)

The chemical shifts are given as ppm in δ values with TMS (0 ppm) is internal standard. Coupling constants (J) are in cps.

Examples 4 to 10

Following the procedures of the foregoing Examples, the compounds of the following Table I according to formula V were obtained.



V

TABLE 1

Ex. No.	R_1	R_2	R_3	R_4	HX
4	methyl	methyl	methyl	pivalyloxymethyl	HNO_3
5	methyl	methyl	*n*-propyl	"	HNO_3
6	methyl	methyl	phenyl	"	
7	ethyl	ethyl	β-cyclo-pentylethyl	"	HCl
8	R_1R_2N piperidyl-1		benzyl	"	HNO_3
9	hexahydro-1H1 azepin-1-yl		methyl	"	
10	R_1 methyl	R_2R_3N— pyrrolidylidene-2		"	HNO_3

In the Table II below are listed the physical constants of the compounds of Table I and the reaction conditions are shown:

TABLE II

	Amide halide preparation					Rotation $[\alpha]_D^{20}$ in ethanol (96%)
Ex. No.	Halogenating agent	Solvent	Reaction time in h.	Recrystallized from	M.P. °C.	
4	$COCl_2$	Toluene	2.5	Acetone-ether	146.5—147	+137
5	$COCl_2$	Toluene	20	Acetone-ether	165—167	+128
6	$(COCl)_2$	Ether	2	Acetone-water	112—112.5	+110
7	$COCl_2$	Toluene	24	Acetone-ether	151—151.5	+100
8	$COCl_2$	Toluene	3	Acetone-ether	148—148.5	+185
9	$COCl_2$	Toluene	4.5	Acetone water	125—126	+154
10	$COCl_2$	Toluene	3	Acetone ether	159—160	+183

Example 11

Pivaloyloxymethyl 6-(N-piperidino-phenylacetamidino-N)-penicillanate nitrate

To a stirred solution of phosphorous pentachloride (2.1 g.) in dry, alcohol-free chloroform (20 ml.) were added quinoline (2.3 ml.) and, after cooling to −10°C., pivaloyloxymethyl benzylpenicillinate (4 g.). After stirring for 15 minutes at −10°C., the solution was poured on to an ice cold saturated aqueous solution of sodium bicarbonate with vigorous stirring. After stirring for 30 minutes, the organic phase was separated and dried over magnesium sulphate at 0°C. After filtration, piperidine (1.7 ml) was added to the filtrate at −15°C. The solution was kept at 0°C for one hour and evaporated *in vacuo*. The residue was triturated with ether (200 ml). The solid piperidine hydrochloride was removed by filtration and the filtrate was evaporated. The resulting oily residue was triturated with petroleum ether (3 × 50 ml) and finally distributed between dilute hydrochloric acid (100 ml.) with a pH of about 3 and ether (50 ml.). The aqueous phase was separated, made alkaline to a pH of about 7.5 and extracted with ether.

To the dried ethereal phase was added a solution of concentrated nitric acid (0.2 ml.) in ethanol (2.5 ml.) with stirring. The precipitate formed was triturated with ether and crystallized from acetone-ether to yield a product with a melting point of 144—147°C. The IR spectrum was identical with that of the compound of Example 8 in Table I.

Example 12

Pivaloyloxymethyl 6-N,N-dimethyl-pivalamidino-N'-penicillanate

To a solution of N,N-dimethylpivalamide (3.9 g.) in dry toluene (15 ml.) was slowly added phosphorous pentachloride (6.9 g.) in dry toluene (75 ml.) at 0°C.. The reaction mixture was stirred for 1.1/4 hours at room temperature. The precipitate was filtered off and washed with toluene and ether. A suspension of the resulting crude amide chloride (4.g.) in dry chloroform (60 ml.) was slowly added to a solution of pivaloyloxymethyl 6-aminopenicillanate (6.6 g.) and triethylamine (14 ml.) in dry chloroform (60 ml.) at −50°C. with stirring. The temperature was kept at −20°C. for half an hour and then raised to 0°C. in the course of 15 to 20 minutes. The solution was evaporated *in vacuo* and the residue treated with ether (300 ml.). After filtration to remove triethylamine hydrochloride, the filtrate was extracted with dilute hydrochloric acid (150 ml. at a pH of about 3). The aqueous phase was made alkaline to a pH of about 7.5 and the oily phase formed was extracted with ether (2 × 100 ml.). The ethereal phase was dried and evaporated *in vacuo*, leaving an oil which was triturated with water (100 ml). The solid form was filtered off. It had a melting point of 74 to 76°C. and could not be further purified.

NMR spectrum (10% w/v $CDCl_3$)

$N{=}C{-}C(CH_3)_3$		9H	s	at 1.20	
$O{-}C{-}C(CH_3)_3$ (‖ O)		9H	s	at 1.23	
$C_{(2)}(CH_3)_2$		3H 3H	s s	at 1.49 at 1.63	
$N(CH_3)_2$		6H	s	at 2.85	
$C_{(3)}H$		1H	s	at 4.44	
$C_{(6)}H$		1H	d	at 5.37	(J=4)
$C_{(5)}H$		1H	d	at 5.50	(J=4)
OCH_2O	ABq	1H 1H	d d	at 5.78 at 5.89	(J=5.5) (J=5.5)

Example 13

Pivaloyloxymethyl 6-[α-(hexahydro-1H-azepin-1-yl)-β-methoxy-ethylideneamino]-penicillanate

A. *Ethyl methoxythioacetate.* Ethyl methoxyacetimidate hydrochloride (37.7 g.) was stirred in pyridine (45 ml.) at −20°C. Hydrogen sulphide (17 g.) was passed into the suspension, whereupon it was stirred for two hours at 0°C., poured onto an aqueous saturated sodium chloride solution (100 ml.) at 0°C., and extracted with ether (2 × 50 ml.). The ethereal phase was extracted with 0.1 N hydrochloric acid until the pH of the aqueous phase was about 5. After extraction with ice-water (2 × 50 ml.) the ethereal phase was dried and distilled to yield the pure compound with a boiling point of 60—61°C./14 mm Hg.

B. *N-Methoxythioacetylhexamethyleneimine.* Ethyl methoxythionacetate (13.4 g.) was added to hexamethyleneimine (22.4 ml.) with stirring and cooling with ice-water. The solution was kept at room temperature overnight and then distilled. The boiling point was 99—101°C./0.15—0.25 mm Hg.

C. *Methyl iodide complex of N-methoxythioacetylhexamethyleneimine.* Methyl iodide (6.2 ml.) was slowly added to a solution of N-methoxythioacetylhexamethyleneimine (14 g.) in acetone (25 ml.). The solution was kept at room temperature for 16 hours. The complex was precipitated by the addition of a few crystals, sucked off, and washed with acetone and ether. The melting point of the crude product was 102—104°C..

D. *Pivaloyloxymethyl 6-[α-(hexahydro-1H-azepin-1-yl)-β-methoxyethylideneamino-penicillanate.* To a solution of pivaloyloxymethyl 6-aminopenicillanate (3.3 g.) and N,N-diisopropylethylamine (3.4 ml.) in chloroform (35 ml.) at 0°C. were added 3.3 g. of the above-mentioned compound and the solution was kept at 0°C. overnight. The chloroform was removed *in vacuo* and the residue triturated with ethyl acetate (50 ml.). After filtration, the filtrate was evaporated *in vacuo* and the residue dissolved in ether (75 ml.), which was extracted with dilute hydrochloric acid (75 ml., pH~3). The aqueous phase was made alkaline to a pH of about 7.5. The oil which separated was taken up in ether. After drying the ether was removed *in vacuo* leaving an oil which did not crystallize.

NMR spectrum (10% w/v $CDCL_3$)

$C(CH_3)_3$	9H	s	at 1.23	
$C_{(2)}(CH_3)_2$	3H	s	at 1.50	
	3H	s	at 1.64	
$CH_2—CH_2—$ $CH_2—CH_2—$	8H	m	at 1.60	
OCH_3	3H	s	at 3.37	
$—CH_2$ \ N— / $—CH_2$	4H	m	at 3.47	
$CH_3O—CH_2—$ ABq	1H	d	at 4.07	(J=12)
	1H	d	at 4.20	(J1=2)
$C_{(3)}H$	1H	s	at 4.38	
$C_{(6)}H$	1H	d	at 5.35	(J=4)
$C_{(5)}H$	1H	d	at 5.52	(J=4)
OCH_2O ABq	1H	d	at 5.78	(J=5.5)
	1H	d	at 5.90	(J=5.5)

Example 14

Pivaloyloxymethyl 6-[α-(hexahydro-1H-azepin-1-yl)-β-hydroxyethylideneamino]-penicillanate

A. *Ethyl hydroxythionacetate* was prepared from ethyl hydroxyacetimidate hydrochloride according to the directions given in Example 13. The boiling point was 50—53°C./10 mm Hg.

B. *N-Hydroxythioacetylhexamethyleneimine.* Ethyl hydroxythionacetate (18.8 g.) was slowly added to hexamethyleneimine at 0°C. with stirring. The solution was kept at room temperature overnight. It was dissolved in ether (150 ml.) and extracted with dilute hydrochloric acid (100 ml. pH of about 2) and water 50 ml.). The ethereal phase was dried and used directly for the next step.

C. *Methyl iodide complex of N-hydroxythioacetylhexamethyleneimine.* Methyl iodide (8 ml.) was added to the ethereal solution. Next day the solid was filtered and recrystallized from ethanol-ether to give the pure compound with a melting point of 80°C.

D. *Pivaloyloxymethyl 6-[α-hexahydro-1H-azepin-1-yl)-β-hydroxyethylideneamino]-penicillanate.* A solution of pivaloyloxymethyl 6-aminopenicillanate (2.7 g.), N,N-diisopropylethylamine (2.8 ml.) and the above-mentioned compound (2.6 g.) in dry chloroform (30 ml.) was kept at 0°C. for 16 hours. The yellow solution was evaporated *in vacuo* and the residue triturated with ethyl acetate (50 ml.). After filtration, the ethyl acetate was removed *in vacuo* and the residue distributed between ether (50 ml.) and dilute hydrochloric acid (50 ml., pH about 3). The aqueous phase was separated, filtered, and made alkaline to a pH of about 7.5. The oily layer formed was taken up in ethyl acetate and dried. Evaporation *in vacuo* left an oil which did not crystallize.

NMR spectrum (10% w/v $CDCl_3$)

$C(CH_3)_3$	9H	s	at 1.22		
$C_{(2)}(CH_3)_2$	3H	s	at 1.53		
	3H	s	at 1.64		
$CH_2—CH_2—$ $CH_2—CH_2—$	8H	m	ca. 1.65		
$CH_2—$ N $CH_2—$	4H	m	ca. 3.50		
$—O—CH_2—C=$	2H	s	at 4.15		
$C_{(3)}H$	1H	s	at 4.42		
$C_{(6)}H$	1H	d	at 4.58	(J=4)	
$C_{(5)}H$	1H	d	at 5.50	(J=4)	
$O—CH_2—O$ ABq	1H	d	at 5.77	(J=6)	
	1H	d	at 5.88	(J=6)	

Example 15

6-(N,N-Dimethyl-benzamidino-N)-penicillanic acid

To a solution of N,N-dimethylbenzamide dimethyl acetal (4.7 g.) in dry ether (100 ml.) was slowly added trimethylsilyl 6-aminopenicillanate (6.9 g.) in dry ether (75 ml.) at −10°C. with stirring was continued for 2 1/2 hours at 0°C. The precipitate which formed was filtered off, washed with ether and stirred for 5 hours at 0°C. with 30 ml. of water. After filtration, the filtrate was freeze-dried to give a while amorphous powder, soluble in water. Thin layer chromatography ("Merck" (registered Trade Mark) silica gel HF_{254}) was performed in the following solvent systems: *n*-butanol-ethanol-water (8:2:2), $R_f = 0{,}10$ and *n*-propanol-water (7:3), $R_f = 0{,}24$.

NMR spectrum (10% w/v D_2O)

$C_{(2)}(CH_3)_2$	3H	s	at	1.54	
$C_{(2)}(CH_3)_2$	3H	s	at	1.72	
$N(CH_3)_2$	3H	s	at	3.10	
$N(CH_3)_2$	3H	s	at	3.45	
$C_{(3)}H$	1H	s	at	4.30	
$C_{(6)}H$	1H	d	at	5.01	(J=4)
$C_{(5)}H$	1H	d	at	5.24	(J=4)
	5H	m	at	7.4—7.9	

Example 16

Pivaloyloxymethyl 6-(N-morpholino-phenylacetamidino-N')-penicillanate

22 ml. of a solution of phosgene in dry toluene, containing 2.2 g. of phosgene, was slowly added to a solution of 4-(phenylthioacetyl)morpholine (3.3 g.) in dry toluene (25 ml.) with stirring and ice-cooling. Stirring was continued for 3 hours at room temperature, whereupon the amide chloride formed was quickly isolated by filtration with suction, washed with ether and kept in an exsiccator.

The crude amide chloride (2.1 g.) was dissolved in dry chloroform (60 ml.) and slowly added to a solution of pivaloyloxymethyl 6-aminopenicillanate (2.65 g.) and triethylamine (2.24 ml.) in the same solvent (24 ml.) at −40°C. with stirring. The temperature was raised to 0°C. during 3/4 hour. After evaporation *in vacuo*, the residue was triturated with acetone (25 ml.). The precipitate formed was filtered off and the filtrate evaporated *in vacuo*. The oily residue was taken up in ether (50 ml.) and extracted with diluted hydrochloric acid (50 ml. at a pH of about 3). The aqueous phase was made alkaline with sodium bicarbonate (pH about 7.5 and extracted with ethyl acetate (2 × 50 ml.). The organic phase was dried and evaporated *in vacuo*. The crystalline residue was recrystallized from acetone (15 ml.) water (10 ml.) and dissolved in ice-cold diluted hydrochloric acid (pH∼ 2.5, 75 ml.). The solution was filtered with "Dicalite" (registered Trade Mark) filter aid and made alkaline with sodium bicarbonate. The crystalline precipitate was filtered off, washed with water, and recrystallized from acetone-water to yield the analytically pure product with a melting point of 124—125°C. $[\alpha]_D^{20}$: +93° (c=1, 96% ethanol).

Example 17

Pivaloyloxymethyl 6-(N-morpholino-4'-methoxyphenylacetamidino-N')-penicillanate p-toluenesulfonate

56 ml. of a solution of phosgene in dry toluene, containing 4.5 g. of phosgene, was slowly added to a solution of 4-(4'-methoxyphenylthioacetyl)morpholine (7.5 g.) in dry toluene (45 ml.) with stirring and ice-cooling. Stirring was continued for 20 hours at room temperature. The amide chloride (5.3 g.) was filtered off, washed with ether, and dissolved in dry chloroform (110 ml.).

This solution was slowly added to a solution of pivaloyloxymethyl 6-aminopenicillanate (3.3 g.) and triethylamine (5.1 ml.) in dry chloroform (50 ml.) at −40°C. with stirring. The temperature was raised to 0°C. during 3/4 hour, whereupon the solvent was removed *in vacuo*. The residue was triturated with acetone (75 ml.). The precipitate was filtered off and the filtrate evaporated *in vacuo*. The oily residue was dissolved in ether (100 ml.) and extracted with diluted hydrochloric acid (100 ml. at a pH of about 2.5). The aqueous phase was filtered with "Dicalite" filter aid, made alkaline with sodium bicarbonate, and extracted with ethyl acetate (3 × 50 ml.).

After drying and evaporation *in vacuo* of the organic phase the residue was redissolved in diluted hydrochloric acid (35 ml., pH~3) at 0°C. and filtered with "Dicalite". By addition of a solution of sodium *p*-toluenesulfonate (1.1 g.) in water (10 ml.) the crystalline salt was precipitated. It was recrystallized from methanol-water and from acetone to yield the analytically pure compound with a melting point of 188—188.5°C. $[\alpha]_D^{20}$: +144° (c=1, 96% ethanol).

Example 18

Pivaloyloxymethyl 6-(N-morpholino-2'-methoxyphenyl-acetamidino-N')-penicillanate nitrate.

A. *Methyl iodide complex of 4-(2'-methoxyphenylthioacetyl)morpholine.* 4-(2'-Methoxyphenylthioacetyl)morpholine (14.2 g.) and methyl iodide (5.3.ml.) in acetone (50 ml.) was stirred for 20 hours. The precipitate formed was filtered off and washed with acetone and ether. The melting point was 145—146.5°C.

B. *4-[2'-methoxy-α-(methylthio)styryl]morpholine.* To an ice-cold solution of the crude product (7.8 g.) in dry chloroform (80 ml.) was added triethylamine (2.8 ml.). The solution was left at room temperature for 20 hours and evaporated *in vacuo*. The residue was triturated with ether (250 ml.), filtered from triethylammonium iodide, and evaporated to leave an oil.

C. *Pivaloyloxymethyl 6-(N-morpholino-2'-methoxyphenylacetamidino-N')-penicillanate nitrate.* A solution of the crude oil (5.6 g.) and pivaloyloxymethyl 6-aminopenicillanate (6.6 g.) in ether (100 ml.) was evaporated *in vacuo* for 4 days in order to remove the methyl mercaptan formed during the reaction. The residue was taken up in ether (100 ml.) and extracted with diluted hydrochloric acid (100 ml. at a pH of about 3). The aqueous phase was filtered with "Dicalite", made alkaline (pH~7.5), and extracted with ethyl acetate (150 ml.). The organic phase was dried and evaporated *in vacuo* to leave an oil, which was redissolved in diluted hydrochloric acid (100 ml., pH~3) and extracted with ether (25 ml.). The acid aqueous phase was filtered with "Dicalite" and made alkaline (pH~7.5). The solid formed was removed, triturated with water (50 ml.), and dried.

To a solution of the solid product in ether (125 ml.) was slowly added a solution of concentrated nitric acid (0.19 ml.) in isopropanol (2 ml.) (caution!) with stirring and cooling. The precipitate was recrystallized from acetone-ether and methanol-ether to yield the analytically pure product with a melting point of 150°C. $[\alpha]_D^{20}$: +236° (c=1, 96% ethanol).

Example 19

Pivaloyloxymethyl 6-(N-morpholino-4'-chlorophenyl-acetamidino-N')-penicillanate

A. *Methyl iodide complex of 4-(4'-chlorophenylthioacetyl)morpholine.* A solution of 4-(4'-chlorophenylthioacetyl)morpholine (10.2 g.) and methyl iodide (3.75 ml.) in acetone (70 ml.) was stirred for 24 hours at room temperature. The precipitate formed was filtered off and washed with acetone and ether. The melting point was 155—157°C.

B. *4-[4'-chloro-α-(methylthio)styryl]morpholine.* To an ice-cold solution of the crude complex (2.0 g.) in dry chloroform (20 ml.) was added triethylamine (0.7 ml.). The solution was left at room temperature for 20 hours and evaporated *in vacuo*. The residue was triturated with ether (75 ml.), filtered from triethylammonium iodide and evaporated to leave an oil.

C. *Pivaloyloxymethyl 6-(N-morpholino-4'-chlorophenylacetamidino-N')-penicillanate.* A solution of the crude oil (1.3 g.) and pivaloyloxymethyl 6-aminopenicillanate (1.65 g.) in ether (15 ml.) was evaporated *in vacuo* for 100 hours in order to remove the methyl mercaptan formed during the reaction. The residue was dissolved in ether (50 ml.) and

extracted with diluted hydrochloric acid (50 ml. at a pH of about 2.5). The aqueous phase was filtred with "Dicalite", made alkaline with sodium bicarbonate, and extracted with ethyl acetate (75 ml.). The organic phase was dried over magnesium sulfate and evaporated *in vacuo* to leave an oil, which was dissolved in methanol (8 ml.) and precipitated by addition of water (2 ml.). After recrystallization from methanol-water the pure product had a melting point of 115—115.5°C. $[\alpha]_D^{20}$: +84° (c=1, 96% ethanol).

Example 20

Pivaloyloxymethyl 6-(N,N-diethyl-2-phenoxyacetamidino-N')-penicillanate nitrate

A. *N,N-Diethyl-2-phenoxythioacetamide.* To a solution of N,N-diethyl-2-phenoxyacetamide (36 g.) in pyridine (125 ml.) was added phosphorus pentasulfide (14.7 g.). The mixture was refluxed for 20 hours with stirring, cooled to room temperature, and filtered. The filtrate was evaporated and the oily residue distilled *in vacuo*. The boiling point was 129—131°C./0.4 mm. Hg.

B. *Methyl iodide complex of N,N-diethyl-2-phenoxythioacetamide.* A solution of N,N-N,N-diethyl-2-phenoxythioacetamide (14.3 g.) and methyl iodide (4.35 ml.) in acetone (70 ml.) was left at room temperature for 24 hours and evaporated *in vacuo*. The oily residue was crystallized by trituration with ether (150 ml.). After recrystallization from isopropanol-ether the melting point was 90.5—91.5°C.

C. *Pivaloyloxymethyl 6-(N,N-diethyl-2-phenoxyacetamidino-N')-penicillanate nitrate.* A solution of the complex above (3.65 g.), pivaloyloxymethyl 6-aminopenicillanate (1.65 g.) and N,N-diisopropylethylamine (1.72 ml.) in dry chloroform (30 ml.) was left at room temperature for 65 hours and thereafter evaporated *in vacuo*. The residue was triturated with ethyl acetate (15 ml.) and filtered. The filtrate was evaporated *in vacuo* and the residue taken up in ether (50 ml.), filtered and extracted with diluted hydrochloric acid (50 ml. at a pH of about 3). The aqueous phase was filtered with "Dicalite", made alkaline with sodium bicarbonate, and extracted with ether (150 ml.).

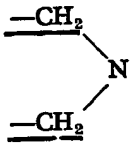
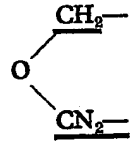
The etheral phase was dried and treated with a solution of concentrated nitric acid in isopropanol at 0°C. with stirring. The precipitate was recrystallized twice from acetone-ether to yield a pure product with a melting point of 120°C. $[\alpha]_D^{20}$: +152° (c=1, 96% ethanol).

Example 21

Pivaloyloxymethyl 6-(N-morpholino-caprylamidino-N')-penicillanate

110 ml of a solution of phosgene in dry toluene, containing 8.8 g of phosgene, was added to 4-octanoylmorpholine (17.2 g) in toluene (100 ml) and left at room temperature for 20 hours. After evaporation *in vacuo* the residue was dissolved in 70 ml of dry chloroform and slowly added to a solution of triethylamine (24 ml) and pivaloyloxymethyl 6-aminopenicillanate (6.6 g) in chloroform (60 ml) at −20°C. with stirring. The temperature was raised to 0°C. during an hour. After evaporation *in vacuo* the residue was triturated with ether (250 ml). The precipitate formed was filtered off, and the filtrate concentrated to 100 ml *in vacuo* and extracted with diluted hydrochloric acid (100 ml at a pH of about 2). The aqueous phase was made alkaline (pH=7.5) and extracted with ether (50 ml). The ethereal phase was extracted with diluted hydrochloric acid (50 ml at a pH of 2). The acid aqueous phase was extracted with ethyl acetate (80 ml) which was dried and evaporated *in vacuo* to leave an oil which did not crystallize.

NMR spectrum (10% w/v $CDCl_3$)

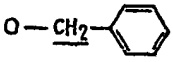
$\underline{CH_3}—\underline{CH_2}—$		3H	m	at	0.88	
$CH_3(\underline{C_5H_{10}})\underline{CH_2}—$		10H	m	at ca.	1.8—1.1	
$\underline{CH_2}—C(=N—)—N<$		2H	m	at ca.	2.32	
$C(CH_3)_3$		9H	s	at	1.22	
$C_{(2)}(CH_3)_2$		3H	s	at	1.49	
		3H	s	at	1.63	
		4H	m	at ca.	3.42	
		4H	m	at ca.	3.63	
$C_{(3)}H$		1H	s	at	4.40	
$C_{(6)}H$		1H	d	at	5.19	(J=4)
$C_{(5)}H$		1H	d	at	5.50	(J=4)
OCH_2O	ABq	1H	d	at	5.78	(J=5.5)
		1H	d	at	5.89	(J=5.5)

Example 22

Benzyl 6-(N,N-diethyl-thiophene-2-carboxamidino-N')-penicillanate

4.8 g of the crude amide chloride prepared from N,N-diethylthiophene-2-carboxamide as described in Example 2, was dissolved in dry chloroform (30 ml) and slowly added to a solution of triethylamine (5.6 ml) and benzyl 6-aminopenicillanate (6.1 g) in chloroform (60 ml) at −50°C. with stirring. The temperature was raised to 0°C. in the course of 3/4 hour. The solution was evaporated *in vacuo* and the semisolid residue triturated with ether (400 ml). After filtration from triethylammonium chloride the filtrate was concentrated *in vacuo* to about 150 ml and extracted with diluted hydrochloric acid (150 ml at a pH of about 2.5). The aqueous phase was filtered with "Dicalite", made alkaline with sodium bicarbonate (pH~7.5), and extracted with ethyl acetate (200 ml). The ethyl acetate was removed *in vacuo*, and the oily residue redissolved in diluted hydrochloric acid (75 ml, pH~2.5), treated with decolourizing carbon, and filtered with "Dicalite". The filtrate was made alkaline (pH~7.5) and extracted with ethyl acetate. The organic phase was dried and evaporated *in vacuo* to leave an oily residue which did not crystallize.

NMR spectrum (10% w/v $CDCl_3$)

$N-(CH_2-\underline{CH_3})_2$	6H	t	at	1.12	(J=7)
$C_{(2)}(CH_3)_2$	3H	s	at	1.39	
	3H	s	at	1.68	
$N-(\underline{CH_2}-)_2$	2H	q	at	3.29	(J=7)
	2H	q	at	3.37	(J=7)
$C_{(3)}H$	1H	s	at	4.47	
$C_{(6)}H$	1H	d	at	4.72	(J=4)
	2H	s	at	5.18	
$C_{(5)}H$	1H	d	at	5.28	(J=4)
	2H	m	at	7.09	
	1H	m	at	7.40	
	5H	s	at	7.37	

Example 23

Cyanomethyl 6-(N,N-dimethyl-butyramidino-N')-penicillanate

N,N-Dimethylbutyramide was converted to the acid amide chloride as described in Example 5 and reacted with cyanomethyl 6-aminopenicillanate in the usual way to give the analytically pure compound with a melting point of 119—120°C. $[\alpha]_D^{20}$: +142° (c=1, 96% ethanol).

Example 24

Benzoyloxymethyl 6-(N,N-dimethyl-butyramidino-N')-penicillanate hydrochloride

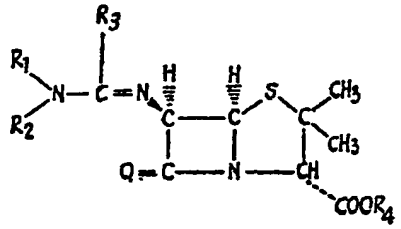
N,N-Dimethylbutyramide was converted to the acid amide chloride as described in Example 5 and reacted with benzoyloxymethyl 6-aminopenicillanate in the usual way and transformed to the hydrochloride. It was recrystallized from methyl ethyl ketone-ethyl acetate. The melting point was 142—143°C.

NMR spectrum (10% w/v $CDCl_3$)

$CH_3—CH_2—CH_2—$	3H	t	at	1.11	(J=7)
$CH_3—CH_2—CH_2—$	2H	m	at	1.81	
$C_{(2)}(CH_3)_2$	3H	s	at	1.49	
	3H	s	qt	1.62	
$CH_3—CH_2—CH_2—$	2H	m	at	2.80	
$—N(CH_3)_2$	3H	s	at	3.38	
	3H	s	at	3.58	
$C_{(3)}H$	1H	s	at	4.62	
$C_{(6)}H$	1H	m	at	5.55	
$C_{(5)}H$	1H	d	at	5.91	(J=4)
$O—CH_2—O$ ABq	1H	d	at	6.05	(J=6)
	1H	d	at	6.13	(J=6)
	3H	m	at	7.59	
	2H	m	at	8.08	

WHAT WE CLAIM IS:—

1. An amidino-penicillanic acid derivative of the general formula:



(1)

in which R_1, R_2 and R_3 each represent an aliphatic hydrocarbon radical, a mono- or bicyclic aryl radical, an aralkyl radical, a cycloalkyl radical, a cycloalkyl-alkyl radical, a heterocyclic radical or a heterocyclically substituted alkyl radical; R_1 and R_2 when taken together with the nitrogen atom may represent a ring system; R_1 and R_3 when taken together with the N—C atoms may represent a ring system; R_1, R_2 and R_3 are optionally substituted; R_4 represents a hydrogen atom or an unsubstituted or substituted alkyl or aralkyl radical; and pharmaceutically acceptable salts thereof.

2. A compound as claimed in claim 1, wherein R_1, R_2 and R_3 are substituted with one or more halogen atoms or alkyl, hydroxy, alkoxy, alkylthio, acyl, carboxy, carbalkoxy, carbamyl, carbamido, cyano, sulphonyl, amino- or substituted amino radicals.

3. A compound as claimed in Claim 1, wherein R_1, R_2 and R_3 are substituted with one or more carbocyclic aryloxy, carbocyclic arylthio, or azido radicals.

4. A compound as claimed in Claim 1 in which R_1 and R_2 represent a C_1—C_7 alkyl radical, R_3 represents an unsubstituted or substituted aralkyl radical, and R_4 represents hydrogen; and acyloxymethyl esters thereof.

5. A compound as claimed in Claim 1 in which R_1 and R_2 represent a C_1—C_7 alkyl radical, R_3 represents a phenoxymethyl radical, and R_4 represents hydrogen; and acyloxymethyl esters thereof.

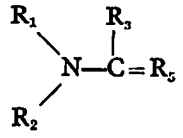
6. A compound as claimed in Claim 1 in which R_1 and R_2 when taken together with the nitrogen atom represent an unsubstituted or substituted saturated heterocyclic ring having from 5 to 8 carbon atoms, and R_4 is a hydrogen or an alkanoyloxymethyl radical having from 3 to 8 carbon atoms.

7. An amidino-penicillanic acid derivative of the general formula defined in Claim 1, substantially as hereinbefore described in any one of Examples 1 to 8, or 11.

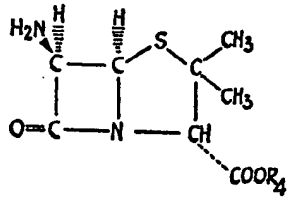
8. An amidino-penicillanic acid derivative of the general formula defined in Claim 1, substantially as hereinbefore described in any one of Examples 9, 10 or 12 to 15.

9. An amidino-penicillanic acid derivative of the general formula defined in Claim 1, substantially as hereinbefore described in any one of Examples 16 to 24.

10. A process for the preparation of a compound of the general formula defined in Claim 1, in which an acid amide halide, an acid amide dialkyl sulphate complex or an acid amide acetal or thioamide acetal or acid thioamide alkyl halide complex or similar reactive derivative of an amide or a thioamide of the general formula:



in which R_1, R_2 and R_3 have the meanings defined in Claim 1, and R_5 stands for an oxygen or sulphur atom, is reacted with a 6-aminopenicillanic acid derivative of the general formula:

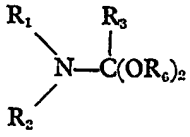


in which $COOR_4$ is an ester group, or with a silyl ester of 6-aminopenicillanic acid, whereafter, if desired, the reaction is followed by a cleavage of the ester to form the free acid.

11. A process as claimed in Claim 10 in which R_1, R_2 and R_3 have the meanings defined in Claim 1 and 2.

12. A process as claimed in Claim 10 in which R_1, R_2 and R_3 have the meanings defined in Claims 1 and 3.

13. A process for the preparation of a compound of the general formula defined in Claim 1, in which a silyl ester of 6-aminopenicillanic acid is reacted with an amide acetal of the general formula:



in which R_1, R_2 and R_3 are as defined in Claim 1, and R_6 is a C_1—C_7 alkyl radical, whereafter the silyl ester of the reaction product is hydrolysed or alcoholysed to form the compound defined in Claim 1 in which R_4 is a hydrogen atom.

14. A process as claimed in Claim 13, in which R_1, R_2 and R_3 have the meanings defined in Claims 1 and 2.

15. A process as claimed in Claim 13, in which R_1, R_2 and R_3 have the meanings defined in Claims 1 and 3.

16. A process for the preparation of a compound of the general formula defined in Claim 1, in which an amine of the formula HNR_1R_2, in which R_1 and R_2 have the meanings defined in Claim 1, is reacted with a reactive derivative of a 6-acylamino-penicillanic acid ester.

17. A process as claimed in Claim 16, in which R_1 and R_2 have the meanings defined in Claims 1 and 2.

18. A process as claimed in Claim 16, in which R_1 and R_2 have the meanings defined in Claims 1 and 3.

19. A process for the preparation of a compound of the general formula defined in Claim 1, substantially as hereinbefore described in any one of Examples 1 to 8, or 11.

20. A process for the preparation of a compound of the general formula defined in Claim 1, substantially as hereinbefore described in any one of Examples 9, 10 or 12 to 15.

21. A process for the preparation of a compound of the general formula defined in Claim 1, substantially as hereinbefore described in any one of Examples 16 to 24.

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